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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/315,292	05/20/1999	CLARENCE FRANK BENNETT	ISIS-3561	6344

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EXAMINER	
BOWMAN, AMY HUDSON	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 10/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/315,292	BENNETT ET AL.	
	Examiner	Art Unit	
	Amy H. Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *66,70-75 and 78-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *66, 70-75 and 78-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 8/10/2006 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 5/10/2006 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant has added claims 78-82. Therefore, claims 66, 70-75 and 78-82 are pending in the application.

Response to Arguments--Claim Rejections - 35 USC § 103(a)

Claims 66 and 70-75 stand rejected under 35 U.S.C. 103(a), as being unpatentable over Kole et al. (U.S. 5,627,274), in view of Nyce et al. (WO 96/40266) and Nicklin et al. (WO 98/09633), for the reasons of record set forth in the office action mailed 5/10/2006.

Applicant has cancelled claims 67-69, obviating the rejection against these claims.

Applicant asserts that Kole teaches oligonucleotides to redirect splicing, not to degrade target mRNAs, as taught by Nyce and Nicklin. Applicant concludes that one making oligonucleotides that do not promote RNase H cleavage would not look to a

reference that teaches oligonucleotides that promote RNase H cleavage to determine what chemical modifications to use. Contrary to applicant's assertion, Kole, Nyce, and Nicklin each teach modified antisense oligonucleotides. Regardless of the fact that Kole teaches such oligonucleotides to redirect splicing, one would still incorporate the instantly recited chemical modifications into the antisense oligonucleotides of Kole because the modifications were known in the art to enhance the resistance of antisense oligonucleotides to nucleases. Furthermore, Kole et al. teaches 2'-O-methyl modifications, which further demonstrates that Kole recognized the value of 2'-modifications, despite the alleged difference in mechanism. This is because 2'-modifications were known to enhance the activity of antisense oligonucleotides.

Applicant further asserts that Nicklin teaches a long series of 2'-modifications and that there is no motivation to select the specific 2'-modification now claimed. The list of chemical modifications taught by Nicklin et al. are all alleged by Nicklin to be useful to enhance oligonucleotide activity, all of which are preferred because they enhance activity. Specifically, 2'-O-methoxyethyl is a modification that was known in the art to enhance activity, as evidenced by Nicklin. One would have been motivated to incorporate such a modification into the antisense oligonucleotides of Kole and would reasonably expect for the modification to benefit stability of the oligonucleotides of Kole.

Furthermore, as evidenced by the 35 U.S.C. 103(a) rejection below, the invention of the above claims is considered obvious even in absence of the Kole et al. reference.

New Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 66, 70-75 and 78-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyce et al. (WO 96/40266), in view of Nicklin et al. (WO 98/09633).

The invention of the above claims is drawn to a method of administering an oligonucleotide into the lung of a mammal, comprising aerosolizing the oligonucleotide wherein the aerosol particles have a size of about 1 to about 5 microns, and introducing the aerosolized oligonucleotide into the lung of the mammal, wherein the sugar moiety of at least one nucleoside unit is a 2'-O-methoxyethyl, and the oligonucleotide is taken up by at least one cell type in the lung. The oligonucleotide is in an aqueous media such as sterilized, pyrogen free water or saline solution or in a saline solution or a powder. The invention is further drawn to a method of increasing uptake into lung cells of a phosphorothioate containing oligonucleotide delivered by pulmonary administration into lung cells comprising incorporation of a 2'-O-methoxyethyl modification into the oligonucleotide.

Nyce et al. teach that respirable antisense oligonucleotides can be formulated to be liquid or solid (see page 10). Liquid compositions comprise the antisense compound and sterile, pyrogen free water or saline solution (see page 9, for example). Nyce et al.

teach that suitable formulations for delivery include powders (see page 12). Nyce et al. teach that respirable antisense oligonucleotides can be formulated into powders and effectively delivered with a metered dose inhaler. Nyce et al. teach methylphosphonate and phosphorothioate linkages to render respirable antisense oligonucleotides more stable *in vivo* (see page 7).

Nyce et al. teach that particles comprised of antisense compound should be of respirable size that is particles of a size sufficiently small to pass through the mouth and larynx upon inhalation and into the bronchi and alveoli of the lungs. Nyce et al. teach that in general, particles ranging from about .5 to 10 microns in size are respirable (see page 10). Therefore, Nyce et al. teach respirable particles "about 1 to about 5 microns", as instantly recited.

Nyce et al. teach a method of administering the aerosolized antisense oligonucleotides to animals *in vivo* (see page 16, for example) and teach uptake of the oligonucleotide in the lungs.

Nyce et al. do not teach 2'-O-methoxyethyl modifications.

Nicklin et al. teach antisense oligonucleotides and teach that modification of antisense oligonucleotides confers increased nuclease resistance, increased uptake into cells, and increased binding affinity for the RNA target (see page 2). Nicklin et al. teach 2' modifications including 2'-alkoxyalkoxy, 2'-O-methoxyethyl, and 2'-O-dialkylaminooxyalkyl modifications. Nicklin et al. teach phosphorothioate, methylphosphonate, and non-phosphorous containing linkage modifications (see pages 4 and 5).

It would have been obvious to incorporate 2'-O-methoxyethyl modifications, as taught by Nicklin et al. into the antisense oligonucleotides taught by Nyce et al.

One would have been motivated to incorporate 2'-O-methoxyethyl modifications because Nicklin et al. teach that such modifications confer increased nuclease resistance, increased uptake into cells, and increased binding affinity for the RNA target. Since Nyce et al. teach other modifications, such as incorporation of phosphorothioates, in order to render the respirable antisense oligonucleotides more stable *in vivo*, one would have been motivated to incorporate 2'-O-methoxyethyl modifications as well since they were also known in the art to enhance oligonucleotide activity, as evidenced by Nicklin et al.

Finally, one would have a reasonable expectation of success to that the chemical modifications taught by Nicklin et al. would benefit the antisense oligonucleotides of Nyce et al. because each of the instantly recited modifications were known in the art at the time the invention was made to enhance the activity of antisense oligonucleotides, as evidenced by Nicklin et al. and Nyce et al.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is 571-272-0755.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Amy H. Bowman
Examiner
Art Unit 1635

JAMES SCHULTZ, PH.D.
PRIMARY EXAMINER